In The Claims

Please cancel Claims 80 and 85 without prejudice or disclaimer of the subject matter contained therein.

Please amend the following Claims:

1. (Currently Amended) A DNA-binding molecule ~~capable of sequence specific binding~~ which binds specifically to a minor groove of double-stranded DNA, ~~characterized in that it comprises~~ comprising at least two sequence specific DNA-binding elements, covalently linked to each other in tandem orientation by an amphipathic, flexible linker molecule, wherein at least one of said DNA binding elements is ~~being~~ non-proteinaceous.

2. (Currently Amended) The DNA-binding molecule according to claim 1 wherein at least one of the DNA-binding elements comprises an oligomer comprising one or more organic heterocyclic amino-acid residues.

3. (Currently Amended) The DNA-binding molecule according to claim 2 wherein each organic heterocyclic residue has at least one annular nitrogen, sulphur or oxygen.

4. (Currently Amended) The DNA-binding molecule according to claim 2, wherein said heterocyclic residue is chosen from pyrrole, imidazolem triazolem pyrazole, furan, thiazolem thiophene, oxazolem pyridine, ~~or~~ and ~~derivatives of~~ any one of these compounds ~~wherein one or more of the heteroatoms are~~ having one or more substituted heteroatoms ~~by a substituent which is DNA-binding or non-DNA binding~~.

5. (Currently Amended) The DNA-binding molecule according to claim 4, wherein ~~at least one oligomer includes~~ said

heterocyclic residues are chosen from the group consisting of N-methylpyrrole (PY), ~~and/or~~ 3-hydroxy N-methylpyrrole (HP) and~~/or~~ N-methylimidazole.

6 - 50. (Canceled)

51. (Currently Amended) A ~~Process~~ process for binding double-stranded DNA in a sequence-specific manner, comprising contacting a DNA-target sequence within said DNA with a DNA-binding molecule according to claim 1, in conditions allowing said binding to occur.

52. (Currently Amended) ~~Process~~ The process according to claim 51 which is carried out *in vivo*, *in vitro* or *ex vivo*.

53. (Currently Amended) ~~Process~~ The process according to claim 52 which is carried out in a cell.

54. (Currently Amended) ~~Process~~ The process according to claim 53, wherein said cell is eukaryotic.

55. (Currently Amended) ~~Process~~ The process according to claim 53, wherein said cell is prokaryotic.

56. (Currently Amended) ~~Process~~ The process according to claim 54, wherein said cell is a vertebrate cell, an invertebrate cell, a plant cell.

57. (Currently Amended) ~~Process~~ The process according to claim 54, wherein said cell is a mammalian cell, an insect cell, or a yeast cell.

58 - 68. (Canceled)

69. (Currently Amended) A ~~Process~~ process for modulating chromosome function in a eukaryotic cell, comprising

the step of contacting a genomic DNA element comprising a binding site mediating chromosome function, with a molecule according claim 1 and ~~having the capacity to bind~~ which binds in a sequence-specific manner to said element, said step of contacting being carried out in conditions permitting binding of said ~~compound~~ molecule to said element, wherein the binding modulates chromosome function.

70. (Currently Amended) A process for modulating the function of a DNA element in a eukaryotic cell, comprising the step of contacting a genomic ~~DNA element so-called~~ <<chromatin responsive element>> (CRE), with a molecule according to claim 1 and ~~having the capacity to~~ which binds in a sequence-specific manner to said CRE, said step of contacting being carried out in conditions permitting chromatin remodeling of the CRE by said molecule ~~compound~~, wherein said chromatin remodeling of the CRE alters the activity of one or more other modulated DNA elements ~~, so-called <<moduldulated DNA elements>>~~ in the genome.

71. (Currently Amended) A ~~Cell~~ cell containing a ~~compound~~ DNA-binding molecule according to any one of claims 1 to ~~50~~ 5.

72. (Currently Amended) The ~~Cell~~ cell according to Claim 71, wherein said ~~compound~~ DNA-binding molecule binds the DNA-minor groove.

73 - 78. (Canceled)

79. (Currently Amended) A ~~Pharmaceutical~~ pharmaceutical composition comprising ~~a compound~~ the DNA-binding molecule according to claim 1 in association with a physiologically acceptable excipient.

80. Cancelled

81. (Currently Amended) A DNA-binding molecule ~~Compound~~ according to claim 1 which is fluorescent or fluorescently labeled.

82. (Currently Amended) The DNA-binding molecule ~~Compound~~ according to Claim 81, wherein the fluorescent label is a fluorescent dye ~~such as~~ selected from the group consisting of fluorescein, dansyl, Texas red, isosulfan blue, ethyl red, malachite green, rhodamine and cyanine dyes.

83 - 85. (Canceled)

Please add new claim 86 as follows:

86. (New) A method of treating genetic disorders, said method comprising administering to a subject in need of such treatment a pharmaceutically acceptable amount of the pharmaceutical composition of claim 79.

REMARKS

Claims 1-5, 51-57, 69-72, 79-82 and 85 are pending in the subject application. By this Amendment, applicants have amended claims 1-5, 51-57, 69-72, 79, 81 and 82, cancelled claims 80 and 85 without prejudice, and added new claim 86. Accordingly, claims 1-5, 51-57, 69-72, 79, 81, 82 and 86 are presented for the Examiners reconsideration.

Support for new claim 86 appears, *inter alia*, at least on page 27 of the application as filed.

Informalities

In Section 2 of the January 16, 2003 Office Action, the Examiner objected to the disclosure because of the following informalities:

a) the continuing information paragraph at page 1 of the specification is incomplete in missing the status of the CIP parent application, and

b) page 34 has four lines of text at the top and the rest of the page is blank. If the application goes to issue this will confuse the printer as it is unclear whether test is missing or the blank is intentional and serves a purpose.

In response, applicants have amended the specification to update the status of the parent application. As to page 34, only the four lines of text are intended. Thus, applicants request that the Examiner make an appropriate notation in the file to prevent any confusion.

Rejection Under 35 U.S.C. § 101

In Section 4 of the January 16, 2003 Office Action, the Examiner rejected claim 85 under 35 U.S.C. 101 alleging that the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. Accordingly, the

Examiner withdrew claim 85 has been withdrawn from consideration.

In response, applicants canceled Claim 85, which should render this rejection now moot.

Rejection under 35 U.S.C. § 112, first paragraph

Written Description

In Section 5 of the January 16, 2003 Office Action, the Examiner rejected claims 70 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner stated that claim 70 is drawn to a process for ''chromatin remodeling of the CRE'' by the DNA binding molecule of claim 1 wherein the ''chromatin remodeling ... alters the activity of one or more other DNA elements, so-called ''modulated DNA elements'' in the genome''. The Examiner noted that the specification at page 27 provides the basis for this claim but alleged that it does not define the ''CRE'' as to its location or nucleotide sequence and does not teach alteration of ''the activity of one or more other DNA elements''. The Examiner also noted that Example 6 at pages 49-51 describes chromatin remodeling and sequence-specific topoisomerase II cleavage mediated by oligopyrroles, but alleged that the ''chromatin response element'' is not mentioned nor are the recited other ''DNA elements'' identified or mentioned. In addition to enablement, the Examiner noted that the first paragraph of 112 requires a ''written description'', and as set forth by the Court in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one skill in the art ''with reasonable clarity'' that as of the filing date applicant was in possession of the claimed invention. The Examiner concluded by acknowledging

that applicant was in possession of a ''chromatin remodeling'' process as described in Example 6 but alleged that the specification does not support ''remodeling of the CRE alters the activity of one or more other DNA elements'' as recited in claim 7.

In response, applicants respectfully traverse this rejection of claim 70, and defer to the Guidelines for examination of patent applications under 35 U.S.C.§ 112, first paragraph for the written description requirement (January 5, 2001), which state that the burden is on the Examiner to establish a *prima facie* case of failure to comply with the written description requirement, which can be done by providing reasons why a person skilled in the art at the time of filing of the application would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure in the application as filed.

The Examiner has not furnished any specific reasons why the skilled artisan would not deem that the inventor had in fact possession of a process for modulating the function of a DNA element in a eukaryotic cell using chromatin remodeling that alters the activity of one or more modulated DNA elements.

Furthermore, under Part II 1. of the Guidelines it is stated that:

> The absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. §112, ¶ 1, for lack of adequate written description.

Applicants submit that chromatine remodeling that alters the activity of one or more modulated DNA elements were well known procedures in the art at the time of filing this application and a detailed procedure was exemplified at least in Example 6 of the present specification.

Thus, a person skilled in the art can easily ascertain from the art and Example 6 that the inventors had possession of the subject matter set forth in Claim 70. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Indefiniteness - claims 1-5, 51-57, 69-72, 79-82 and 85

In Section 6 of the January 16, 2003 Office Action, the Examiner rejected claims 1-5, 51-57, 69-72, 79-82 and 85 under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleged:

(A) the claims are confusing due to the recitation ''capable of'' in claim 1 and ''having the capacity to'' in claim 70 because it is unclear whether a process or a property is intended. The Examiner suggested using direct language for clarity, e.g., replace ''capable of ... binding'' and ''having the capacity to bind'' with --binds--.

(B) in claim 4, if ''derivatives of any of these compounds'' is to be included in the Markush group, ''or'' in line 4 should be --and--. The Examiner stated that the ''or'' indicates that ''residues'' and ''derivatives'' are separate groups from which to choose, i.e., they may not be mixed.

(C) claim 4 is indefinite because ''derivatives'' is an indeterminate term which is not defined in the claim or in the specification. For example, its possible meanings range from a single atom of a recited heterocyclic residue to a very large multimer molecule to which a heterocyclic residue is attached. It is noted that ''substituent which is DNA-binding or non-DNA-binding'' is not definitive.

(D) claim 5 is confusing in the use of ''and/or'' in the Markush group. The Examiner suggested to delete ''or'' at both occurrences.

(E) in claim 70 the phrase ''so-called'' renders the claim indefinite because it is unclear as to whether the ''CRE'' is a response element or something else by another name. The Examiner suggested to delete ''so-called'' as it is clear from the specification

(F) claim 71 is indefinite in depending from canceled claims.

(G) claims 70-72 and 79-82 lack antecedent basis in claim 1 for ''said compound'' because claim does not recite ''compound'' and the intended antecedent cannot be determined.

(H) in claim 82 the phrase ''such as'' renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by ''such as''), thereby rendering the scope of the claim(s) unascertainable.

In response, applicants have amended the claims to more clearly recite their invention. Specifically, ''capable of'' has been removed in Claim 1 and Claim 70 and replaced by the term ''binds;'' proper Markush language has been inserted into claims 4 and 5; ''so-called'' and ''such as'' have been deleted from claims 70 and 82; proper antecedent basis is now found for claims 70 to 72 and 79 to 82; and claims 51, 69, 71, 79 and 81 have been amended to depend from non-canceled claims.

With respect to the term ''derivatives'' in claim 4, Applicants have amended claim 4 to clarify that applicants' residues include those with substituted heteroatoms, as described at least on page 9, 2nd paragraph of the specification. Therefore, Applicants submit that this term is in fact definite.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. 102(b): Anticipation over WO 98/37066

In Section 7 of the January 16, 2003 Office Action, the Examiner rejected claims 1-5, 51-57, 70-82 under 35 U.S.C. 102(b) as allegedly anticipated by WO 98/37066. The Examiner alleged that the claim 1 minor groove DNA binding molecule characterized in that it comprises at least two sequence specific DNA binging elements covalently linked to each other in tandem orientation by an amphipathic, flexible linker molecule at least one of which is non-proteinaceous is disclosed at page 55, claims 13-14 and page 17, lines 1-4 of the reference ; the embodiment of claim 2 wherein at least one of the DNA binding elements comprises an oligomer comprising one or more organic heterocyclic amino acid residues is disclosed at page 2, lines 13-15 of the reference identifying imidazole and pyrrole heterocyclic residues ; the embodiment of claim 3 wherein each organic heterocyclic residue of claim 2 has at least one annular nitrogen, sulphur or oxygen is disclosed at page 2, lines 13-15 of the reference identifying imidazole and pyrrole heterocyclic and other residues which have annular nitrogens ; the embodiment of claim 4 wherein the heterocyclic residue of claim 2 is chosen from the group comprising pyrrole and imidazole and derivatives thereof is disclosed at page 10, lines 10-16 of the reference as pyrrole and imidazole ; the embodiment of claim 5 wherein in at least one oligomer of claim 4 includes heterocyclic residues chosen from a group comprising 3-hydroxy-N-methylpyrrole and others is disclosed at page 10, lines 11-12 of the reference as 3-hydroxy-N-methylpyrrole.

The Examiner also alledged that the claim 51 process for binding double-stranded DNA in a sequence-specific manner comprising contacting a DNA target sequence with a DNA binding molecule of claim 1 in conditions allowing binding to occur is disclosed at page 33, Example 7 of the reference; the embodiments of claims 52-54, 56 and 57 wherein the process is carried out *in vivo* in a cell which is a eukaryotic,

vertebrate, mammalian cell is disclosed at page 6, lines 9-30 of the reference; the embodiments of claims 71-72 wherein the claims are drawn to a cell containing a ''compound'' of claim 1, interpreted as the DNA binding molecule of claim 1, and wherein the compound binds the DNA minor groove are disclosed at page 6, lines 9-11 of the reference; the embodiment of claim 79 wherein the ''compound'' of claim 1 is in a pharmaceutical composition with a physiologically acceptable excipient and the embodiment of claim 80 wherein the claim ''compound'' is ''for therapy'' is disclosed at page 7, lines 4-11 of the reference; and the embodiment of claims 81 and 82 wherein the ''compound'' is fluorescently labeled and the label is fluorescein are disclosed at page 8, line 2 of the reference.

In response, applicants respectfully traverse the rejection for reasons that follow. Claim 1 of the present invention recites that the ''at least two sequence specific DNA-binding elements are covalently linked to each other **in tandem orientation**...''. At least page 6 of the specification explains what tandem orientation means, which is:

> The DNA-binding elements are linked in a tandem manner, i.e., consecutive DNA-binding elements are linked in the same orientation with respect to each other, for example in a head-to tail configuration. In the case of DNA-binding elements which have amino and carboxy termini, for example pseudopeptide polyamide molecules, the amino terminus of a first DNA-binding element is tethered via the linker to the carboxy-terminus of a second-DNA binding unit. The individual DNA-binding elements are thus oriented in the same direction, greatly facilitating the binding of the molecule to the DNA. In the context of the invention ''tandem'' means in the same orientation and ''inverted'' means in the opposite orientation.

WO 98/37066 discloses at least two specific DNA binding elements covalently linked to each other in inverted orientation. There is simply no disclosure in WO 98/37066 to tether the at least two specific binding elements in tandem location.

Indeed, as illustrated in Figures 1 and 6 of WO 98/37066, attached **Exhibits 1 and 2**, respectively, the first two C=O molecules after the ''linker'' are oriented to the outside of the molecule and hence are attached in an inverted orientation.

In contrast, as shown in Figure 1 of this application attached as **Exhibit 3**, the orientation of the first two C=O molecules after the linker is different in applicants' molecules; i.e., one C=O is oriented inward and the other outward and thus the at least two DNA binding elements are attached in a tandem orientation.

In conclusion, since WO 98/37066 does not disclose or even suggest a tandem orientation of the DNA-binding elements, the present invention is not anticipated by this reference.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. 102(e): Anticipation over Dervan

In Section 8 of the January 16, 2003 Office Action, the Examiner rejected claims 1-5, 51-57, 71, 72 and 79-82 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by the patent to Dervan et al. (5,998,140). The Examiner alleged that the claim 1 minor groove DNA binding molecule characterized in that it comprises at least two sequence specific DNA binding elements covalently linked to each other in tandem orientation by an amphipathic, flexible linker molecule, is disclosed at column 30, claim 1 with column 5, lines 44-49 of the reference which identifies the amphipathic, flexible linker molecule as -alanine and at column 31, claim 3; the embodiment of claim 2

wherein at least one of the DNA binding elements comprises an oligomer comprising one or more organic heterocyclic amino acid residues is disclosed at column 31, claim 3 of the reference; the embodiment of claim 3 wherein each organic heterocyclic residue of claim 2 has at least one annular nitrogen, sulphur or oxygen is disclosed at column 31, claim 3 of the reference identifying imidazole and pyrrole heterocyclic residues and other residues which have annular nitrogens; the embodiment of claim 4 wherein the heterocyclic residue of claim 2 is chosen from the group comprising pyrrole and imidazole and derivatives thereof is disclosed at column 31, claim 3 of the reference as pyrrole and imidazole; and the embodiment of claim 5 wherein in at least one oligomer of claim 4 includes heterocyclic residues chosen from a group comprising N-methylpyrrole and others is disclosed at column 4, lines 60-63 of the reference as N-methylpyrrole.

The Examiner also alleged that the claim 51 process for binging double-stranded DNA in a sequence-specific manner comprising contacting a DNA target sequence with a DNA binding molecule is directed at column 33, claim 22 and column 34, claim 28 of the reference; the embodiments of claims 52-57 wherein the process is carried out *in vivo* in a cell which is a eukaryotic or invertebrate or mammalian cell or a prokaryotic cell is disclosed at column 15, line 56-column 16, line 5 of the reference; the embodiments of claims 71-72 wherein the claims are drawn to a cell containing a ''compound'' of claim 1, interpreted as the DNA binding molecule of claim 1, and wherein the compound binds the DNA minor groove are disclosed at column 30, claim 1 and column 31, claim 3 of the reference; the embodiment of claim 79 wherein the ''compound'' of claim 1 is in a pharmaceutical composition with a physiologically acceptable excipient and the embodiment of claim 80 wherein the claim ''compound'' is ''for therapy'' are disclosed at column 15, line 66-column 16, line 63 of the reference and the embodiment of claims 81 and 82 wherein the ''compound'' is

fluorescently labeled and the label is fluorescein are disclosed at column 7, lines 24-30 of the reference.

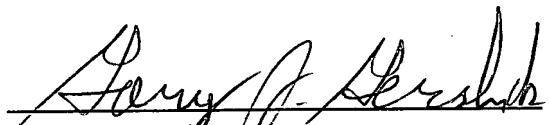
In response, applicants traverse the rejection based on the same arguments as set forth above with respect to WO 98/37066 which are also incorporated herein for this rejection. Dervan et al disclose a minor grove DNA binding molecule comprising at least two specific DNA elements covalently linked to each other in inverted orientation. The Examiner is thus referred to **Exhibit 4**.

Since Dervan et al fails to teach or even disclose a tandem orientation of the at least two specific DNA binding elements, this reference does not anticipate the presently claimed invention.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

No fee, other than the enclosed $465.00 fee for a three-month extension of time is deemed necessary in connection with the filing of this Response. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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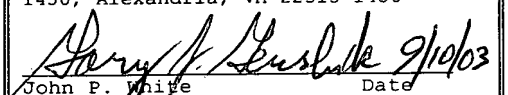

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